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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/320,767	05/27/99	GIANNOUKAKIS N	A32367

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EXAMINER	
CONNELL, Y	

ART UNIT	PAPER NUMBER
1633	4

DATE MAILED: 01/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/320,767	Nick Giannoukakis, et al
Examiner	**Group Art Unit**
Yvette Connell Albert	1633

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-19 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-19 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-19 are rejected under 35 U.S.C 112 first paragraph, because the specification while being enabling for recombinant viral vectors such as adenovirus, lentivirus, and herpes simplex virus-1 comprising nucleic acid molecules encoding inhibitors of IL-1 beta such as interleukin-1 receptor antagonist protein, NF-kappa beta inhibitor and insulin like growth factor-1 protein, and inhibitors of Fas mediated apoptosis such as interleukin-1 receptor antagonist protein, NF-kappa beta inhibitor, and insulin like growth factor-1 protein, to reduce beta cell dysfunction in vitro, does not reasonably provide enablement for the reduction and hence treatment for beta cell dysfunction in an individual. The specification does not enable any person skilled in the art to which it pertains, or to which it is most nearly connected, to make and or use the invention in scope with these claims. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

The claims are drawn towards a method of inhibiting pancreatic beta cell dysfunction and Fas mediated apoptosis by the use of recombinant viral vectors comprising nucleic acid molecules, encoding inhibitors of IL-1beta and Fas-mediated apoptosis, introduced into beta cells. The genetically engineered beta cells, as per the specification, are intended to be transplanted into an individual with a pancreatic disorder so as to reduce IL-1beta mediated beta cell dysfunction and apoptosis, thereby reducing the insulitis associated with pancreatic disorders such as insulin dependent diabetes mellitus (IDDM).

The claims are also drawn towards a mammalian beta cell comprising a recombinant nucleic acid molecule which expresses an inhibitor of IL-1 beta activity. The expressed inhibitor includes interleukin-1 receptor antagonist protein; NF-kappa beta protein; and insulin like growth factor-1 protein, which reduces beta cell dysfunction.

In addition, the claims are drawn to recombinant viral vectors such as adenoviral, lentiviral, and herpes simplex viral vectors, which comprise a nucleic acid molecule encoding an inhibitor of IL-1 beta activity: the inhibitors of which are listed above.

The specification teaches one skilled in the art how to generate recombinant adenoviruses with the appropriate deletions, how to manufacture lentiviruses, how the human islets were isolated and transduced, and how transduced products were detected and evaluated for beta cell function after in vitro treatment with IL-1 beta. The specification also discloses how apoptosis was measured in islets cells in vitro, as well as the effect of IL-1 beta inhibitors in suppressing Fas-triggered apoptosis activation of islets in vitro.

The specification has examples and results which demonstrate that human islets can be infected efficiently with adenoviral vectors, and that they can secrete significant levels of IL-1 receptor antagonist protein.

At the time of filing, there was no confirmed success in any human gene therapy trial, including trials involving a method of reducing beta cell dysfunction in an individual with a pancreatic disorder. "In 1990, the first clinical trials for gene therapy approaches to combat disease were carried out. Although there are more than 200 clinical trials worldwide with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story". (Verma, Inder, M; Somia, Nikunji. Nature 389. 239-242 (1997)).

W. French Anderson, Nature 392. 25-30 (1998) states: Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease.

W. French Anderson (Nature 392 S, 25-30, 1998) teaches that: "the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how in vivo immune defenses can be overcome, and how to manufacture efficiently the vectors that we do make".

At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art.

The physiological art in general is acknowledged to be unpredictable. The field of gene therapy was and remains one of ongoing development. Thus, gene therapy is highly unpredictable.

The specification fails to provide an enabling disclosure for the nucleic acid molecules encoding the inhibitors of IL-1 beta cells and inhibitors of Fas-mediated apoptosis. It is noted on page 18 that a list of potential sources is cited. It is indicated that the nucleic acids can be isolated from a variety of different sources, including but not limited to vertebrate, mammalian and human sources. However, it should be recognized that the isolation of nucleic acids suitable for the instant invention may require extensive and undue experimentation, as it requires different technical considerations and experimental conditions which may not yield the desired final outcome as outlined in the specification.

The specification fails to provide an enabling disclosure for the use of PCR to amplify the desired nucleic acid sequence by failing to give the experimental conditions under which this PCR would take place, the sequences of the two oligonucleotide primers used and how they were manufactured.

The specification fails to provide an enabling disclosure for the use of promoters used in the instant invention. Applicant claims that expression of the sequence encoding the inhibitor of apoptosis can be regulated by any promoter known to act in mammalian, preferably human cells(pg.19). However, applicant is reminded that the regulatory sequences that control gene expression hardly remain active, and there is a tendency for the cells to recognize foreign promoters, especially viral promoters such as SV40 and CMV, and inactivate them by methylation and or other mechanisms. (Anderson, 1998, pg.26).

The specification fails to provide an enabling disclosure for the method of delivery of genes to cells in tissue culture. Several delivery systems are cited on page 25, each with its own advantages and disadvantages. In the absence of a specific gene delivery method cited, the artisan would have had to experiment with several gene delivery systems to determine which system give higher levels of gene expression in pancreatic cells with minimal cell damage.

The specification also fails to teach how many recombinant viral particles would be needed to transfect cells ex vivo, and whether or not the production of these recombinant viral particles would be more or less time consuming depending upon the recombinant viral particle utilized. Applicant must remember that retroviral vectors are biological agents: they can only be made by living cells, as such, biological systems are not the easiest systems in which to carry out good manufacturing practices (GMP) and quality assurance and quality control (QA/QC) procedures. (Anderson, pg.26, 1998). Therefore, one cannot rush or hasten the production of retroviral vectors.

The specification fails to disclose how pancreatic cells would have been extracted and maintained prior to ex vivo transduction. The specification also fails to teach how many cells would be extracted from each donor on each visit, and the frequency with which donors would be required to donate pancreatic cells.

The specification fails to provide an enabling disclosure for the delivery of ex vivo transduced cells to the host. The specification also fails to teach how many pancreatic cells would be transduced ex vivo, before administering in vivo, to reduce beta cell dysfunction in an individual.

The specification fails to teach in the instance that it becomes necessary to administer the pancreatic cells more than once to restore beta cell function (pg. 29), the frequency of administration, and what would be the preferred routes of administration in the case of repeated doses.

The human body has spent many thousands of years learning to protect itself from the onslaught of environmental hazards, including the incorporation of foreign DNA into its genome. In addition, the immune system is designed to recognize and eliminate foreign gene products and cells that produce a foreign protein.

The immune system is still likely to recognize a new or modified protein produced by the therapeutic gene; a newly synthesized normal protein will appear abnormal to an immune system that has never been exposed to it. (Anderson, pg 25, 26, 1998).

The applicant while cognizant of this fact by suggesting the co-administration of immunosuppressants, fails to disclose how much immunosuppressants would be administered and for what period of time, to an individual. Hence, the specification is not enabling because of its failure to teach dosages and frequencies of administration of immunosuppressants.

Without specific guidance, and for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods or use the claimed products as disclosed in the specification.

The quantity of experimentation involved in determining a viable source of nucleic acids, a specific gene delivery system which delivers high levels of expression in cells with minimal damage to the

cells; the number of transfectants which would be therapeutically effective in reducing beta cell dysfunction; the quantity of recombinant viral vectors needed per therapy, and the actual administration of the transductants, involves not only undue experimentation, but also one skilled in the art may not be trained in the surgical procedures as one embodiment of the specification, in the administration of transduced beta cells in situ.

Claim Rejections - 35 U.S.C. § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 13-17 are rejected under 35 U.S.C.102 (b) as being clearly anticipated by Welling et al, 1996. Welling et al discloses a recombinant adenoviral vector comprising a cDNA for human IL-1 receptor antagonist protein.

Applicant discloses a recombinant adenoviral vector comprising a nucleic acid molecule encoding an inhibitor of IL-1 beta activity. The inhibitors included interleukin-1 receptor antagonist protein, NF-kappa beta, and insulin like growth factor-1 protein.

Therefore, the claimed invention was clearly anticipated by Welling et al, since it was known and shown that recombinant adenoviral vectors could be used to transduce an inhibitor of IL-1 beta activity, namely the interleukin-1 receptor antagonist protein.

Conclusion

No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yvette Connell, whose telephone number is 703-308-7942. The examiner can normally be reached on Monday-Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 703-308-0447.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Yvette Connell

December 28, 1999

JOHN L. LeGUYADER
PRIMARY EXAMINER
GROUP ~~1800~~
1600